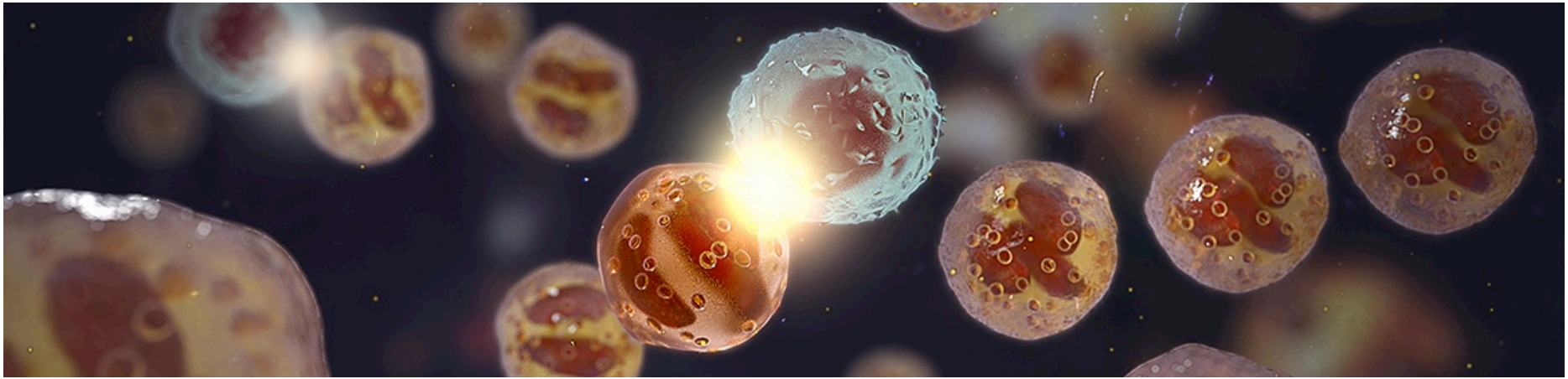
Small trials, historical data: methods and software for decision making

Dominic Magirr

CEN-ISBS Historical data for confirmatory prospective clinical trials – a contradiction? (Part 1)



Content

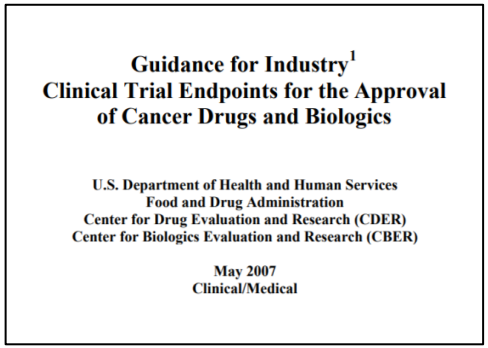
1. Role of historical control data in accelerated approvals in oncology

- How this influences early phase trial design

2. Go/no-go criteria: benchmarking with historical data

- Example
- Software – collaboration with Cytel

Context



Guidance for Industry[1]
Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2007
Clinical/Medical

"In settings where there is no available therapy and where major tumor regressions can be presumed to be attributed to the tested drug, the FDA has sometimes supported ORR and response duration observed in single-arm studies as substantial evidence supporting accelerated approval".

"Objective Response Rate (ORR) is defined as the proportion of patients with tumor size reduction of a predefined amount and for a minimum period".

Examples from 2016
(Blumenthal and Pazdur, 2017)

Drug	Indication
Venetoclax	Chronic lymphocytic leukaemia (17p deletion)
Rucaparib	Ovarian cancer (BRCA mutation positive)
Crizotinib*	Non small cell lung cancer (ROS1-rearranged)
Atezolizumab	Urothelial carcinoma
Pembrolizumab	Head-and-neck squamous-cell carcinoma
Nivolumab	Hodgkin lymphoma

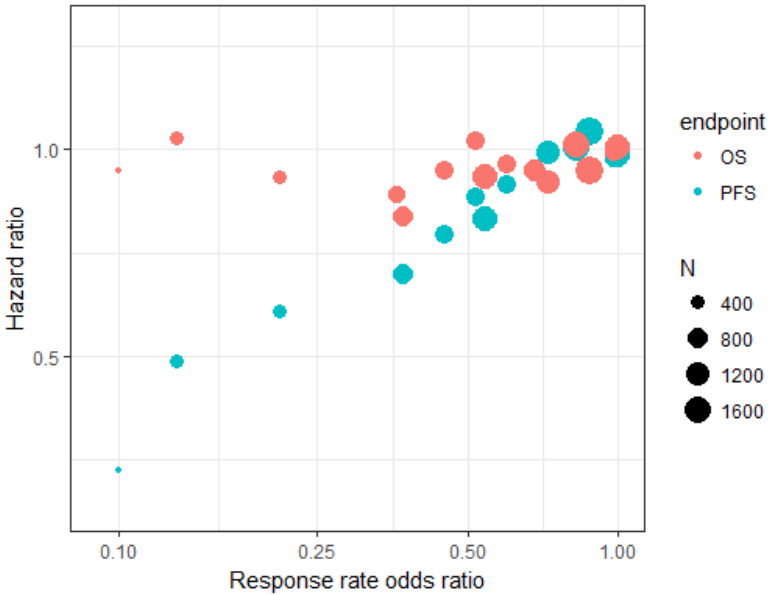
*regular approval

Concerns

1. Does response rate translate to clinically meaningful endpoints?

2. Lack of incentive to test safety and efficacy after accelerated approval.

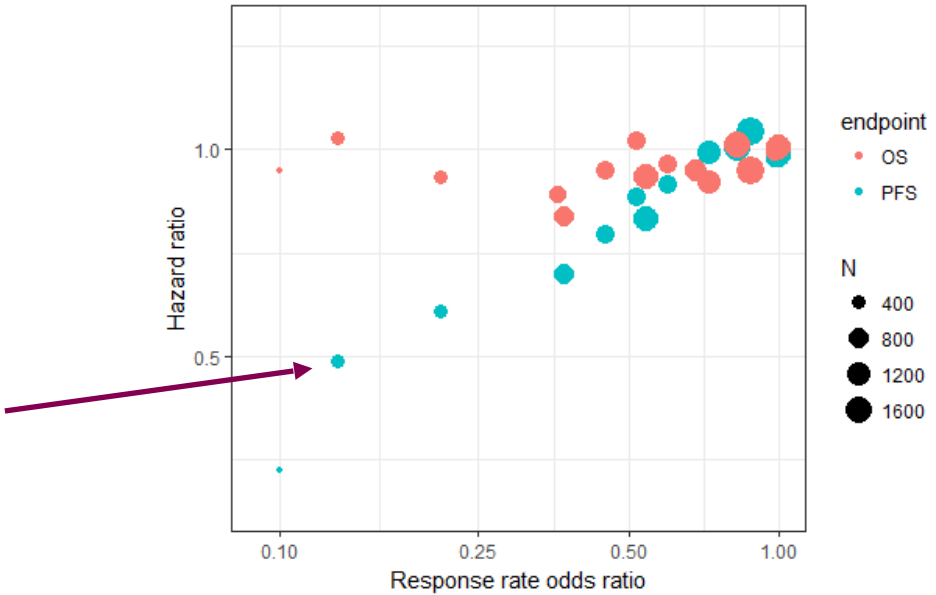
NSCLC data from FDA submissions (Blumenthal et al. 2015)



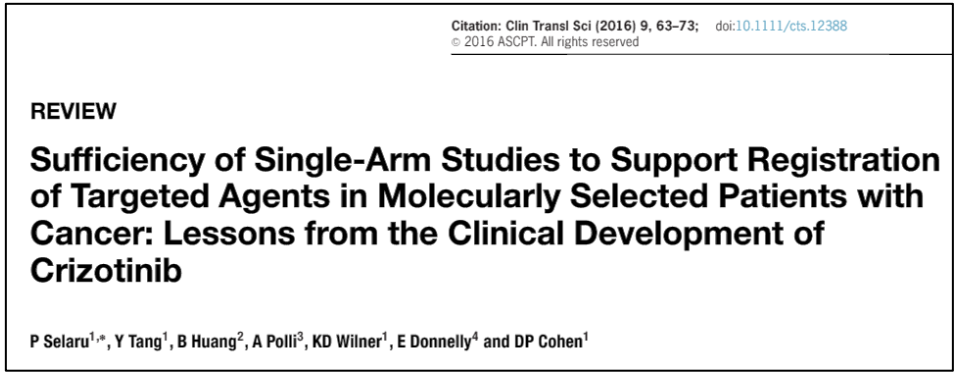
Concerns

1. Does response rate translate to clinically meaningful endpoints?
2. Lack of incentive to test safety and efficacy after accelerated approval.
3. “Successes” have a big impact on early phase trial design.

NSCLC data from FDA submissions (Blumenthal et al. 2015)



Generalizing from success



Citation: Clin Transl Sci (2016) 9, 63–73; doi:10.1111/cts.12388

REVIEW

Sufficiency of Single-Arm Studies to Support Registration of Targeted Agents in Molecularly Selected Patients with Cancer: Lessons from the Clinical Development of Crizotinib

P Selaru[1,*], Y Tang[1], B Huang[2], A Polli[3], KD Wilner[1], E Donnelly[4] and DP Cohen[1]

2009

- First Phase I results (Kwak et al., 2009)
- Responses in NSCLC patients with ALK mutations: 3 out of 10.
- Expected response rate on standard chemotherapy ~10%.

2011

- Accelerated approval.
- Based on response rates of approximately 60% in two single-arm studies (n = 149 and n = 261).

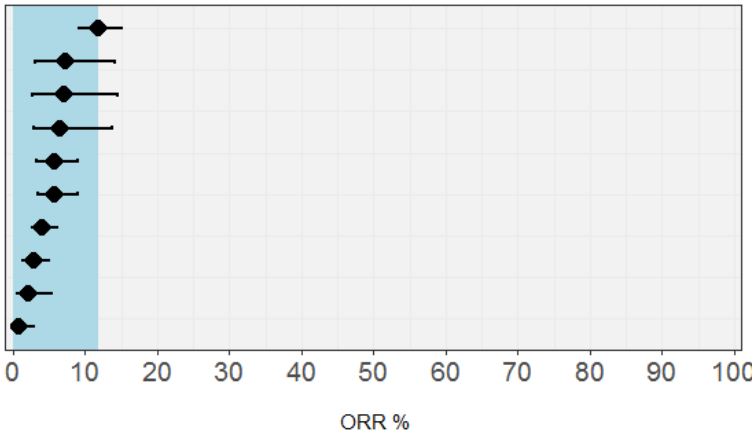
2013

- Full approval.
- Based on randomized study (Shaw, 2013)
- Response rate on chemotherapy arm was 20%

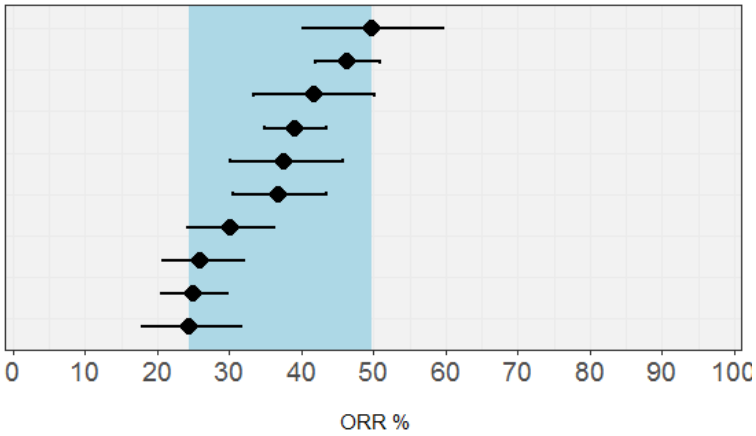
“Signal searching” using single-arm studies and response rate…

…should be challenged in the following two scenarios.

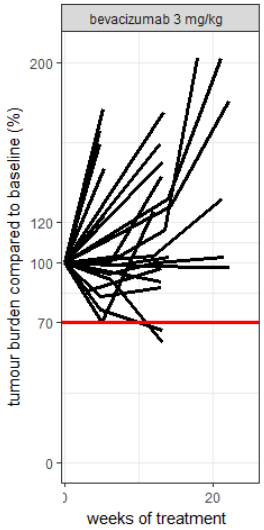
1.



2.



1. When ORR on standard care is close to zero



Illustrative example: based on trial of bevacizumab in metastatic renal cancer. See Yang (2004) for original data.

- Single-arm studies are fine at screening out truly ineffective treatments.

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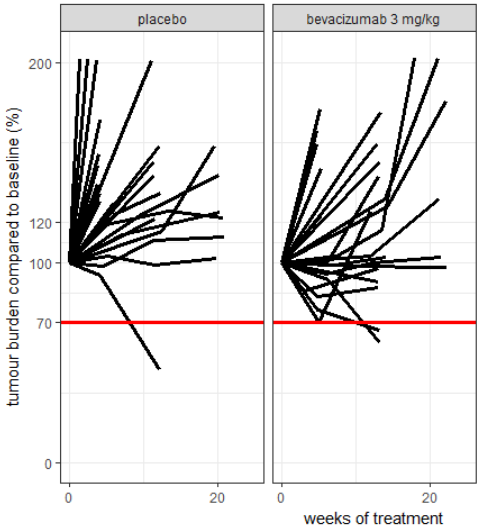

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- But type II error rate can be very large (Karrison, 2007).
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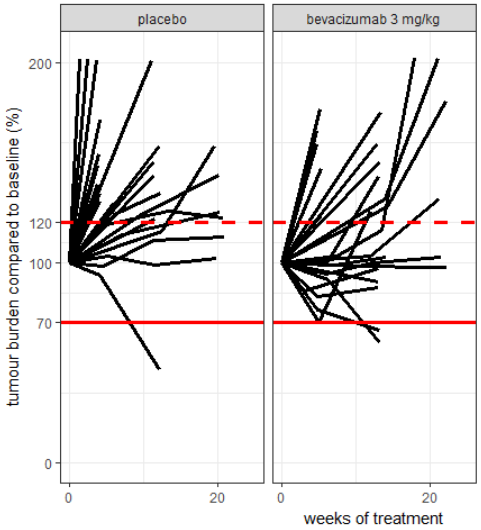

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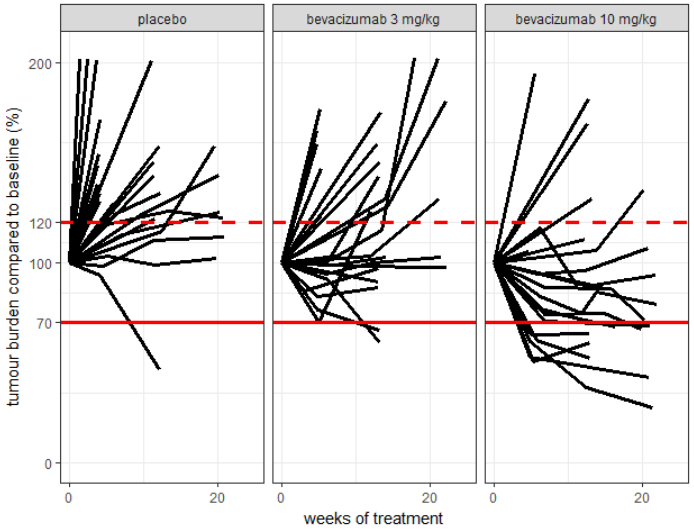

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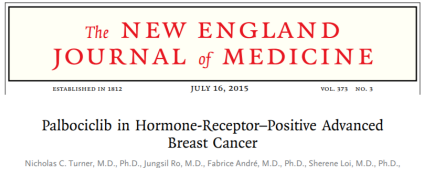
- If acknowledged, the “solution” is to add another threshold (disease control rate) and stick with single-arm design.
- But then we run into between-trial heterogeneity problem.
- This example also demonstrates the benefit of randomized dose-ranging phase 2.

Possible to find similar examples

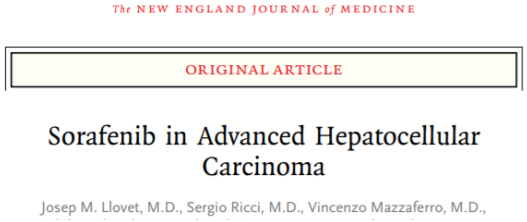

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 16, 2015 VOL. 373 NO. 3

Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer

Nicholas C. Turner, M.D., Ph.D., Jungsil Ro, M.D., Fabrice André, M.D., Ph.D., Sherene Loi, M.D., Ph.D.,

- PFS hazard ratio 0.42 (0.32, 0.56)
- Response rate was 10% versus 6%

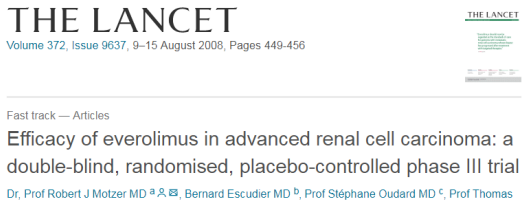

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sorafenib in Advanced Hepatocellular Carcinoma

Josep M. Llovet, M.D., Sergio Ricci, M.D., Vincenzo Mazzaferro, M.D.,

- OS hazard ratio 0.69 (0.55, 0.87)
- Response rate was 2% versus 1%


THE LANCET

Volume 372, Issue 9637, 9–15 August 2008, Pages 449-456

Fast track — Articles

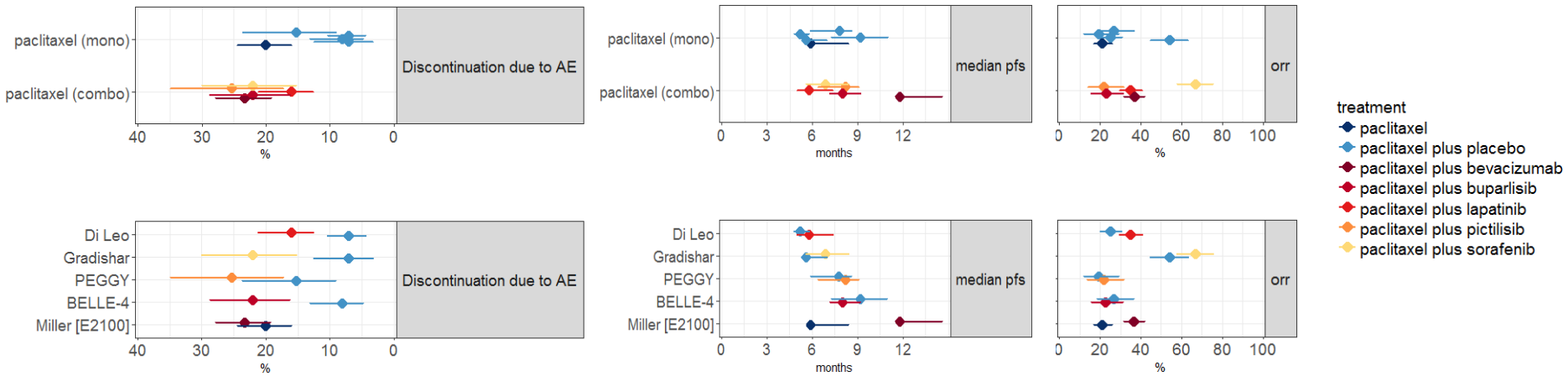
Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial

Dr, Prof Robert J Motzer MD [a], Bernard Escudier MD [b], Prof Stéphane Oudard MD [c], Prof Thomas

- PFS hazard ratio 0.30 (0.22, 0.40)
- Response rate was 1% versus 0%

2. Example where ORR on standard care is not close to zero

Consider combining a new targeted agent with paclitaxel in advanced breast cancer.



- Combination therapy will lead to tolerability issues compared with monotherapy.

- Large between trial heterogeneity relative to most treatment effects.
- Randomized trial required to test efficacy.

Early phase decision making (Frewer, 2016; Lalonde, 2007)

Lower reference value (LRV)

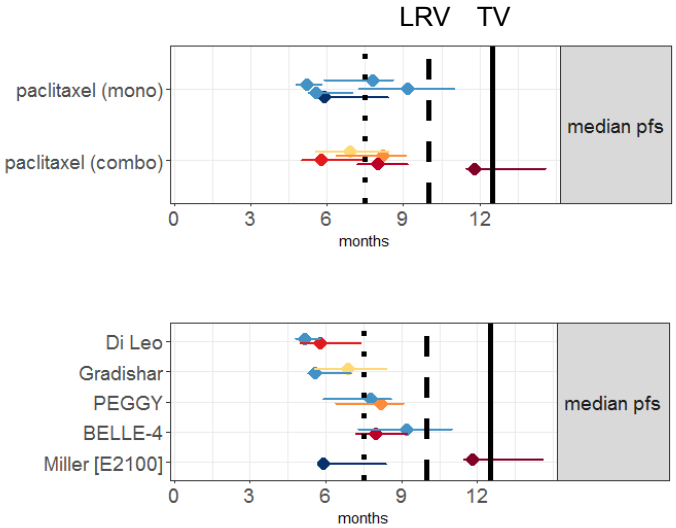
- The lowest level of efficacy that would be considered clinically meaningful.

Target value (TV)

- Desirable level of clinical activity
- Would encourage physicians to switch their patients to the new treatment.

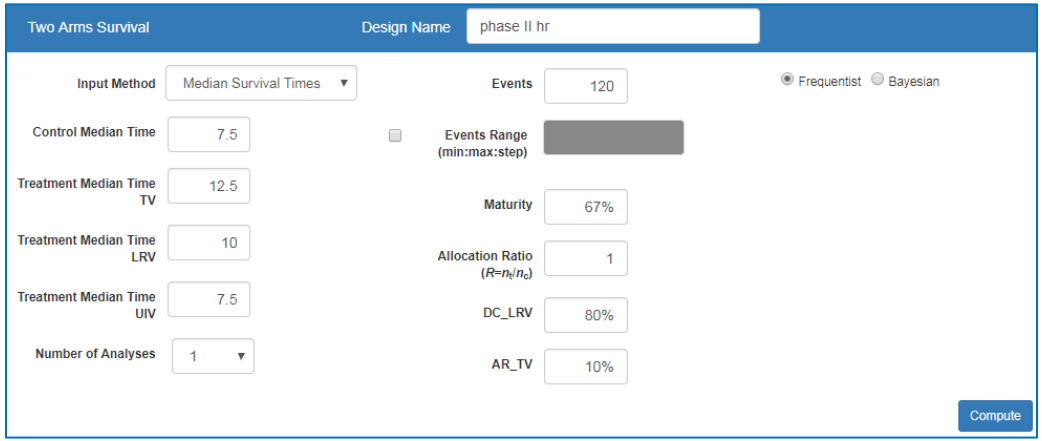
Converting to the hazard ratio scale:

- TV 7.5 / 12.5 = 0.6
- LRV 7.5 / 10 = 0.75

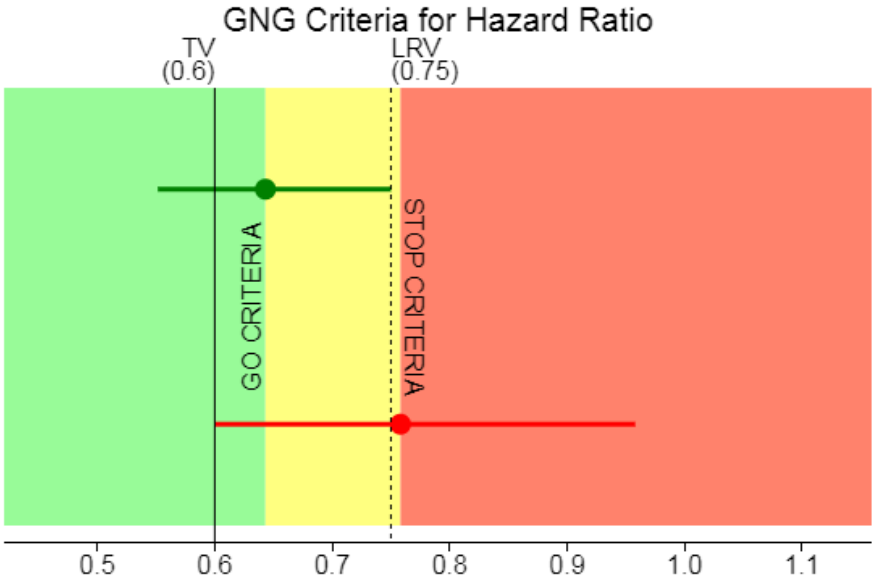


dECiDe

- AstraZeneca and Cytel have co-developed software: Decision making in Early Clinical Development (dECiDe).
- Easy-to-use interface.
- Interim analyses.
- Bayesian version (currently very basic).



Output



Probabilities	Go (0.64)	Consider	Stop (0.76)
Target Value (0.6)	65%	25%	10%
Lower Reference Value (0.75)	20%	32%	48%
User Interest Value (1)	1%	6%	94%

<u>Go decision</u>

- Upper limit of one-sided 80% confidence interval lies below LRV.

<u>Stop decision</u>

- Lower limit of one-sided 90% confidence interval lies above TV.

Summary

Accelerated approvals based on response rates in oncology

- Role of historical data is simple: assumption of minimal activity.
- Single-arm “expansion cohort” studies are ubiquitous.
- Careful presentation of historical data can be used to demonstrate the limitations of this approach to colleagues.

Evidence-based go/no-go criteria

- A three-outcome decision space better reflects complex setting and is more likely to be accepted.
- This means that pre-specified criteria are always applied at the end of the study – a good scientific practice that can be difficult to achieve in early development.
- dECiDe software co-developed by AstraZeneca and Cytel makes it easy to implement.

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